AMENDMENTS TO THE DRAWINGS

The drawings are objected to for the following reasons:

The legend of Figure 12 indicates a Group B, but the figure is labeled with a curve C.

In Figure 15, the curves are not labeled.

Applicants submit replacement sheets for Figures 12 and 15, both clean and marked versions, in the Appendix hereto. These are corrections of typographical errors and find support in the Tables of Figures 5, 10, and 13. Accordingly, no new matter is added.

REMARKS

With this amendment, claims 1-98 have been replaced with claims 99-107. Support for the new claims is found in the original specification and claims as follows.

In order to use standardized terms claim 1 has been amended by exchanging the term "severe congestive heart cause" by the term "severe congestive heart failure" (disclosure for said amendment can be found, e.g., in paragraph [0011] of the patent application is filed).

Furthermore, step a) of the method according to the present invention is now directed to the determination of Big ET-I (1-38) as the first marker. The second marker to be determined in the method according to the present invention is now specified to be N-proANP (1-98) or N-proANP (68-98). Disclosure for said amendment can be found in the claims and in the specification as filed, in particular in paragraph 0031 in connection with paragraphs 0067-0070.

Claim 1 has further been amended by introducing the features of previously filed claims 2, 11 and 17 (cutoff levels of each marker claimed). All other claims have been amended accordingly.

Summary of claimed subject matter

The subject matter of the present invention is a method of predicting the survival outcome of individuals suffering from severe congestive heart failure (CHF). The claimed method involves the determination of the level of two markers, namely Big ET-I (1-38) and N-proANP (1-98) or N-proANP (68-98). The determination of said two markers allows determination of the likelihood of death of an individual from a cardiovascular cause and to categorize these individuals into groups having a high, intermediate or low survival prognosis. The results obtainable by the method according to the present invention are of major importance for the practitioner because it allows him to select the most appropriate therapy for the patient to be treated.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-98 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This ground of rejection is moot as all of claims 1-98 are canceled with this amendment. The Examiner's comments on claims 1-98 have been taken into account in drafting of claims 99-107 with regards to antecedent basis and identification of N-proANP (68-98) as a fragment.

Rejection under 35 U.S.C. § 102(b)

Claims 67, 68, 79-81 and 88 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Selvais, et al. (Eur. J. Clin. Invest. 28: 636, 1998).

This ground of rejection is moot in view of cancelation of the rejected claims. New claims 99-107 are directed to the use of Big ET-I (1-38) and N-proANP (1-98) or N-proANP (68-98) when predicting the survival of patients suffering from severe CHF. The combination is not taught by Selvais, et al.

In view of Applicants' amendment, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 1-98 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Selvais, et al. (J. Cardiac Failure 6: 201, 2000), Selvais, et al. (Eur J. Clin. Invest. 28: 636, 1998), Rousseau, et al. (Circulation 108 (17 Suppl.): IV-556, 2003), Berger, et al. (J. Heart Lung Transplant. 22: 1037, 2003), and Sabatine, et al. (Circulation 105: 1760, 2002).

This ground of rejection is moot in view of Applicants' cancelation of claims 1-98. The references are discussed below with regards to new claims 99-107.

None of the cited references teach the combination of markers as claimed to predict survival outcome of an individual suffering from severe congestive heart failure, wherein severe congestive heart failure is defined as NYHA class III-IV as claimed. For the present claims, Rousseau, et al are considered to be the closest prior art.

Some of the markers used in the method according to present invention, namely Big ET -I and NproANP (68-98), have been described in Rousseau et al. to be suitably used to predict the survival rate in patients suffering from severe congestive heart failure. The authors of said document analysed the individual predictive value of the markers N-ANP 1-25, N-ANP 68-98, BNP, N-BNP, ET-I and Big ET-I in individuals suffering from severe congestive heart failure. Each of these markers was analysed individually for its potential to predict the survival rate in

individuals suffering from severe congestive heart failure. According to Rousseau et al., Big ET -I and ET -I are considered as good independent predictors of survival in patients suffering from severe congestive heart failure. Also the other markers identified in Rousseau et al. with the exception of BNP can be used to predict survival of patients suffering from severe congestive heart failure. From the disclosure of Rousseau et al. it is evident that the person skilled in the art can choose one single marker from a list of potential markers.

In contrast to Rousseau et al., the method according to the present invention requires the determination of ***two markers***, namely Big ET-I (1-38) and N-proANP (1-98) or N-proANP (68-98) and not one marker only as described in Rousseau et al.. In Rousseau et al. it is neither disclosed nor suggested to combine the markers in order to predict the survival outcome in severe congestive heart failure. On the contrary, a person skilled in the art looking at Rousseau et al. would not combine any of the markers disclosed therein, because Rousseau et al. clearly teaches to use the markers independently from each other.

The present invention differs from Rousseau et al. by the use of ***two*** markers, namely Big ET-I (1-38) and N-proANP (1-98) or N-proANP (68-98) fragment. As mentioned above, the markers disclosed in Rousseau et al. were used independently. This is emphasized particularly in line 21 and 22 of Rousseau et al., wherein it is explicitly stated, that the markers are independent predictors.

Another major difference between the subject matter of the present invention and Rousseau et al. is the fact that N-proANP (1-98) is not described in Rousseau et al. to be a suitable marker to predict the survival outcome of individuals suffering from severe congestive heart failure. Rousseau et al. mentions only N-proANP (1-25) and N-proANP (68-98). This is of particular importance, because as shown in the examples and in the figures of the present patent application (see Fig. 10) and discussed below, N-proANP (1-25) is <u>not</u> a good marker in combination with N-proANP (1-98) or N-proANP (68-98) fragment.

The experimental data provided in the present patent application shows that the specific marker combinations of the present invention can be advantageously used to predict survival outcome of individuals suffering from severe congestive heart failure. From the data, it is evident that Big ET-I (1-38) and N-proANP (1-98) or N-proANP (68-98) fragment can be effectively used to determine how long a patient suffering from severe congestive heart failure may survive.

From Fig. 10 it can be deduced that a patient suffering from severe congestive heart failure having levels of Big ET-I (1-38) and N-proANP (1-98) (indicated as "N-proANP") and N-proANP (68-98) fragment above the cut-off value (indicated as "M1 H and M2 H") will survive for about 5 months. In contrast thereto, if the level of said markers are all below said cut-off value (indicated as "M1 L and M2 L"), the individuals suffering from severe congestive heart failure have a high survival rate of more than 91 months. However, if one of the levels of said markers is below its cut-off value and the other marker is above its cut-off value (indicated as "M1 H and M2 L or M1 L and M2 H"), the survival rate is intermediate. This means that patients having these marker levels may survive according to the enclosed table for about 21-22 months. In contrast to these data, other marker combinations cannot be suitably used to predict survival outcome with the same reliability as with the combination of markers claimed in the present invention. For instance, Big ET-I (138) combined with N-proANP (1-25) results in a much lower survival rate when both markers are below the cut-off value. The same observations are true also for other marker combinations as those claimed.

As discussed in the specification at paragraph 0112 (reproduced below):

> The use of Big ET-l(l-38) in combination with N-proANP (1 -98), N-proANP (68 - 98), N-proANP (1 -25), N-proBNP (1 -76), BNP or ET-I did considerably improve the prediction of poor survival (see FIG. 11), when compared to the predictive value of each parameter considered individually (see FIGs. 6 and 7). Indeed, the combination of 2 parameters allows definition of a group of patients with a median survival time that is about twice that of the high risk group determined with a single test (about 5 months versus 10 months). In addition the combination of Big ET-I (1-38) with N-proANP (1-98) also allows the identification of a group with an exceptional good prognosis (over 91 months of median survival).

By practice of the claimed method using two markers, prediction of the survival outcome of patients suffering from severe congestive heart failure is much more reliable than with use of a single marker as taught in the cited art. In addition to a high risk group, by practice of the claimed method, an intermediate risk group can be identified reliably which cannot be done using one marker alone. Furthermore, by using the specifically claimed marker combinations, a low risk group is identified that cannot be reliably identified using one marker or other combinations of markers.

The results reported in the specification are surprising since a person skilled in the art would, in the light of Rousseau et al., assume that all markers disclosed therein can effectively be used as independent predictors. One would not expect that effectiveness in prediction of outcome for NYHA class III-IV individuals could be more accurately predicted by combining two markers, especially for patients having longer survival times. In contrast to the teachings of Rousseau et al. by practice of the claimed invention, the marker combinations as claimed can be used to predict a survival outcome in individuals suffering from severe congestive heart failure with much greater accuracy than by use of individual markers as taught in the prior art.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Mar. 24, 2010

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